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Circadian disruption and metabolic disease: Findings from animal models

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Social opportunities and work demands have caused humans to become increasingly active during the late evening hours, leading to a shift from the predominantly diurnal lifestyle of our ancestors to a more nocturnal one. This voluntarily decision to stay awake long into the evening hours leads to circadian disruption at the system, tissue, and cellular levels. These derangements are in turn associated with clinical impairments in metabolic processes and physiology. The use of animal models for circadian disruption provides an important opportunity to determine mechanisms by which disorganization in the circadian system can lead to metabolic dysfunction in response to genetic, environmental, and behavioral perturbations. Here we review recent key animal studies involving circadian disruption and discuss the possible translational implications of these studies for human health and particularly for the development of metabolic disease.

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Introduction

Circadian rhythms allow organisms to anticipate, rather than react to, daily changes in the external environment and to synchronize their behavioral and physiological processes to predictable environmental changes in order to optimize energy utilization, reproduction, and survival. While some animals evolved to be active during the night (*e.g.* mouse, rat) over the course of evolution, humans have developed to be active predominately during the day. However, unlike other animals, humans are unique in that they often voluntarily shift their activity period to an abnormal time of day, effectively forcing a misalignment between their activity period and their internal circadian clock. Behavioral modification, such as late evening activities, shift work, or jet lag from traveling rapidly across time zones can cause external and internal circadian rhythm disruption which in turn has been linked to metabolic disturbances including, under chronic conditions, obesity, metabolic syndrome, and diabetes as well as other physical and mental disorders.[1–4]

Approximately 15% of Americans are employed as shift workers[5] and are forced to adopt a work-rest schedule that does not match the 24 h solar day, resulting in "circadian misalignment". Shift work has been associated with an increased risk for obesity and its cardio-metabolic consequences.[6–11] Furthermore, the number of people experiencing circadian disruption on a daily or weekly basis is expected to increase as the trend for a non-stop 24 h society spreads and more and more people voluntarily shift to more nocturnal activity. The use of animal models to uncover genetic and environmental links between circadian disruption and metabolic disease is essential for our understanding of the underlying mechanisms and for the development of therapeutic strategies.

In this review, we summarize key findings from animal studies which reveal the relationship between circadian disruption and metabolic disease. We begin by briefly reviewing circadian rhythms and their fundamental role in life processes. Next, we discuss how altering the timing of light cues, such as during shift work, can lead to detrimental effects on metabolism. We then focus on how disruption of the feeding/fasting rhythm may contribute to metabolic dysfunction independent of light cues. As the interaction between the circadian system and metabolism is not unidirectional, we then present evidence demonstrating that metabolic elements are capable of modifying circadian rhythms and gene expression. Indeed, the discovery of key genes and gene networks that are linked to both circadian and metabolic systems, and the use of animal models of genetic circadian disruption has begun to elucidate key mechanisms linking circadian physiology and metabolic function and dysfunction. The final section of this review discusses future implications of utilizing animal models to address important questions concerning circadian disruption and metabolic disease.

Circadian rhythms: in the brain and periphery

In mammals, the master *circadian* (from Latin for "about a day") clock has been identified in the bilaterally paired suprachiasmatic nuclei (SCN) located in the anterior hypothalamus of the brain. The SCN is synchronized to the 24 h day by light signals that stimulate melanopsin-containing retinal ganglion cells,[12] which, in turn, relay light–dark information to the SCN via the retinohypothalamic tract.[13] In this way, the rising and setting of the sun dictates and entrains much of our daily rhythms via the SCN, which then relays time of day information to the rest of the brain as well as peripheral organs, leading to coordinated rhythms and behaviors. Sleep/wake, feeding/fasting and body temperature rhythms are examples of rhythms controlled by the circadian clock and thus synchronized to the 24 h solar day.

In addition to feeding/fasting cycles, metabolically relevant circadian fluctuations involve glucose[14] and insulin. Oral glucose tolerance is impaired in the evening compared to the morning, an effect believed to be due to a combination of both decreased insulin secretion and altered insulin sensitivity in the evening.[15] The 'dawn phenomenon' refers to an elevation in blood glucose levels prior to the onset of the active period that has been well-documented in patients with diabetes and has been also reported in a few studies in normal volunteers.[16,17]

Under normal conditions, molecular and behavioral rhythms remain synchronized by the SCN. As the SCN uses light as a *Zeitgeber* (German for "time giver"), light stimuli given at different circadian times have differential shifting effects on the SCN clock. These responses can be replicated and predictably mapped on a Phase Response Curve (PRC). For example, light occurring early during the